45

Hematopoiesis and Hematopoietic Failure

Eunice S. Wang and Nancy Berliner

HEMATOPOIESIS

Hematopoiesis is the process of formation and development of blood cells. The constituents of peripheral blood arise by a complex and carefully regulated process of ontogeny. The pluripotent hematopoietic stem cell (HSC) maintains itself by self-renewal and undergoes multilineage differentiation to generate the appropriate numbers and types of cells in the circulating blood compartment (Table 45-1). The hematopoietic system is unique in that it is constantly undergoing this full cycle of maturation by which a primitive cell develops into a variety of highly specialized end-stage cells, all of which have different lifespans and occur in different quantities.

The bone marrow must have the capacity to produce cells to compensate for the normal rapid turnover of hematopoietic cells resulting from senescence, normal use, and migration into tissue spaces. It must have a reserve capacity to produce additional cells in response to unusual demands that arise from bleeding, infection, or other stresses. Understanding the repeated cycle of cellular ontogeny and self-renewal that meets these challenges provides important insights into normal and pathologic mechanisms in hematology.

Hematopoietic Tissues

Hematopoiesis commences in the embryonic yolk sac, in which early erythroblasts in blood islands form the first hemoglobinized cells. After 6 weeks' gestation, the fetal liver begins producing primitive lymphocytoid cells, megakaryocytes, and erythroblasts, and the spleen becomes a secondary site of erythropoiesis. Hematopoiesis then shifts to its definitive long-term site in the bone marrow, the principal site for lifelong hematopoiesis in the normal host.

Early in life, all fetal bones contain regenerative bone marrow, but the marrow becomes progressively replaced by fat with age. In adults, active marrow resides only in the axial skeleton (i.e., sternum, vertebrae, pelvis, and ribs) and in the proximal ends of the femur and humerus. Consequently, bone marrow samples, which are needed for many hematologic diagnoses, are usually obtained from the iliac crest or sternum. Under pathologic conditions that stress the capacity of the marrow space, as seen in diseases associated with marrow fibrosis (e.g., myeloproliferative diseases) or in severe inherited hemolytic anemia (e.g., thalassemia major), extramedullary hematopoiesis may be reestablished in sites of fetal hematopoiesis, especially the spleen.

TABLE 45-1 NORMAL VALUES FOR PERIPHERAL BLOOD CELLS

CELL TYPE AND SIZE	MEAN	RANGE
Hemoglobin	Women: 14 g/dL Men: 15.5 g/dL	Women: 12-16 g/dL Men: 13.5-17.5 g/dL
Hematocrit	Women: 41% Men: 47%	Women: 36-46% Men: 41-53%
Reticulocyte count	60,000/μL (1%)	35,000-85,000/μL (0.5-1.5%)
Mean corpuscular volume		80-100 fL
Platelet count	250,000/μL	150,000-400,000/μL
Total white blood cell count	7400/μL	4500-11,000/μL
Neutrophils	4400/μL (40-60%)	1800-7700/μL
Lymphocytes	2500/μL (20-40%)	1000-4800/μL
Monocytes	300/μL (<5%)	200-950 (4-11%)

Stem Cell Theory of Hematopoiesis

All mature hematopoietic cells are hypothesized to originate from a small population of pluripotent stem cells. Comprising less than 1% of all cells in the bone marrow, these cells bear no distinctive morphologic markings and are best defined by their unique functional properties.

Stem cells have two distinctive characteristics. First, they are highly resilient and productive, capable of continuously replenishing huge numbers of granulocytes, lymphocytes, and erythrocytes throughout life. The demand for a continuous, fluctuating supply of blood cells requires a hematopoietic system capable of producing large numbers of selected cells in a short time. For example, overwhelming infection by invading microorganisms triggers the release of neutrophils, whereas hypoxia or acute blood loss leads to increased red blood cell production. Second, HSCs represent a self-renewing cell population that is able to maintain its numbers while providing a continued supply of progenitor cells of many different lineages.

Despite their vast proliferative potential, under normal conditions, most HSCs are quiescent, and few cells undergo expansion or differentiation at any one time. However, their ability to proliferate is striking. Studies with lethally irradiated mice have demonstrated the ability of a few transplanted cells (i.e., spleen colony-forming unit [CFU-S] cells) to regenerate multilineage hematopoiesis.

The signals regulating the differentiation of pluripotent stem cells into committed progenitors are unknown. Data suggest that the first step in lineage commitment is a stochastic (chance)